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# Autonomic Dysreflexia in a Rat Model Spinal Cord Injury and the Effect of Pharmacologic Agents

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The object of this study was to develop a spinal cord injury (SCI) rat model for autonomic dysreflexia (AD), assessing the effect of alpha-adrenergic and calcium channel blockade and to determine the relationship of detrusor-external sphincter dyssynergia (DESD) to the development of AD. A laminectomy was performed in male rats at the T4 or T10 level and a controlled 50 g cm blunt SCI was induced using an impounder. Four weeks after injury, changes in arterial blood pressure and heart rate were monitored while simultaneous cystometry (CMG) and pelvic floor electromography (EMG) were performed in vivo in sham (control) and spinal cord injured rats. The effects of terazosin (0.1 mg/kg), diltiazem (0.5 mg/kg), and oxybutynin chloride (0.1 mg/kg) on hemodynamic changes were assessed independently. Both T4 and T10 SCI rat displayed evidence of DESD (enhanced pelvic floor EMG activity at cystometric capacity) while control rats did not. Only T4 injured rats exhibited evidence of AD, with mean blood pressure elevations from 82.9 ± 13.6 to 93.9 ± 11.3 mm Hg ($P < 0.01$) and a mean heart rate decrease from 332.2 ± 56.5 to 311.1 ± 54.5 beats/min ($P = 0.02$) at cystometric capacity. The intravenous administration of terazosin or diltiazem abolished the AD response during CMG. The administration of oxybutynin exhibited the ability to increase bladder capacity and improve compliance in all 3 groups but did not blunt AD. The rat model of SCI effectively reproduced hemodynamic changes consistent with the AD complex in T4 level SCI but not T10 level SCI animals, despite incomplete lesions. Blockade with either an alpha-1 or a calcium channel antagonist effectively ablated the AD response to bladder distention. Anticholinergic agents had no effect on AD. DESD frequently accompanies autonomic dysreflexia, although the development of AD is not a prerequisite for DESD. 

**Key words: spinal cord injuries, rat, neurogenic bladder, urodynamics, autonomic dysreflexia**

## INTRODUCTION

Autonomic dysreflexia (AD) is a condition which results in paroxysmal hypertension from a severe, unopposed sympathetic discharge. The condition commonly afflicts spinal cord injury patients with lesions above the T7 level as a consequence

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of a stimulus below the level of the injury [Kurnick, 1956]. The development of AD represents a medical emergency, where the consequences may be significant morbidity or death [Kursch et al., 1977]. Unfortunately, those predisposed to the syndrome may experience frequent, recurrent episodes of AD.

AD may occur in response to a variety of stimuli. Many, in fact the most common, sources of such stimuli are genitourinary in origin [Erickson, 1980]. Because the sequelae of AD are severe and potentially life-threatening, it is important for urologists to recognize and treat this entity promptly. Up to this time, management has rested upon the treatment of AD episodes when they develop. Several pharmacologic agents have been described for use in treating the extreme hypertension which occurs with AD.

Historically, nonspecific alpha-adrenergic blockade with phenoxybenzamine has been used as prophylaxis against the development of AD [Scott and Morrow, 1978]. Nifedipine, a calcium channel blocker, has been shown to be effective in treating acute episodes of AD [Dykstra et al., 1987]. To date, no controlled laboratory investigation has been conducted using a selective alpha-1 adrenergic blocking agent or calcium channel antagonist to prophylax against or treat the development of AD.

The development of AD in spinal-cord transected rats, subjected to bladder distention, has recently been documented [Osborn et al., 1990]. We have utilized a rat model of blunt spinal cord injury to further investigate the AD response. In our investigation, we have compared the hemodynamic parameters of high-level to lower-level spinal cord-injured rats subjected to urodynamic testing. We have utilized selective alpha-1 blockade using terazosin and calcium channel antagonism with diltiazem to determine their effect on the development of AD.

## MATERIALS AND METHODS

### Animals

Three separate groups of nine male Sprague-Dawley (Charles River Laboratories, Wilmington, MA) rats were utilized. One group was designated for sham-injury, another for spinal cord injury (SCI) at the T4 level, and the third group for T10 level SCI. Each animal weighed from 250 to 300 g.

### Animal Care

All animals were not subjected to surgery for a minimum of 2 days after their arrival. A 12h:12h light-dark cycle was used, with food and water supplied ad libitum. The research protocol and animal usage in these studies had been approved by our Institutional Animal Care and Use Committee, and adhered to guidelines set forth in the U.S. Health and Human Service's "Guide for the Care and Use of Laboratory Animals." Prophylactic parenteral antibiotic (cefazolin 15 mg/kg) was administered twice daily for 3 days after surgery. Urine pH was monitored twice weekly; an alkalotic urine, indicative of infection, was treated with a 5-day regimen of a parenteral antimicrobial agent. Bladder urine was expressed manually every 8 hours after SCI, to the time the animals emerged from spinal shock. The animals with induced spinal cord injury were supplied with excess bedding material to prevent decubitus ulcer formation, and turned at least twice daily for at least 1 week after SCI.

Animals and pens were inspected daily and cleaned of urinary and fecal contamination.

### Anesthesia

Intraperitoneal pentobarbital (65 mg/kg) anesthesia was induced in all animals. During all surgical procedures, rectal temperature was maintained between 37° and 38°C with a heating pad.

### Surgery

After a sufficient depth of anesthesia was verified, the animal was positioned in a spinal stereotaxic apparatus (David Kopf, Tujunga, CA), with fixation at the ears. The skull was exposed, and stainless-steel jeweler's screws (Small Parts, Miami, FL) were implanted as electrodes for recording the somatosensory-evoked potential (SEP) [Salzman et al., 1988]. Screws were threaded into the skull near the union of the midline with bregma (positive) and lambda (negative) and in the nasal sinus (reference). Stimuli were delivered through a pair of platinum subdermal needle electrodes (Grass Instruments, Quincy, MA) inserted in the hindlimb near the medial malleoulus and plantaris tendon. Constant voltage pulses were delivered at 3 Hz and at an intensity sufficient to elicit a slight twitch in the outer digits (10 to 15 V). SEPs were averaged over a 90-millisecond epoch using 256 trials and a bandpass between 3.2 and 3,2000 Hz. The latency and amplitude of the major negative wave was then measured over three to five trials. The thoracic region of the spine was then exposed, and a laminectomy performed at the T4 or T10 level. The dura mater was left intact. The SEP was then re-evaluated in order to confirm the presence of normal conduction after laminectomy. Animals were excluded from study if the SEP latency increased by more than 2 milliseconds or if the amplitude decreased by more than 50%. Animals with intact responses were then prepared for injury by applying additional fixation at the T-6 or T-12 spinous process using a vertebral clamp, depending on the level of injury to be induced.

### Spinal Cord Injury

The injury device consisted of a hollow steel tube with a nylon impounder at the bottom (0.3 cm diameter at the tip). The impounder was free to move up into the tube but restricted in its downward movement. After being secured to a micromanipulator, the device, with impounder tip fully extended, was lowered onto the exposed dura until contact with the cord caused the impounder to move precisely 0.2 cm up into the tube. At this point, a 10 g weight was dropped from a height of 5 cm (50 gm cm injuries). Sham rats underwent an identical laminectomy at the T10 level without weight drop and confirmed with no SEP changes.

### Neurological Evaluation

All assessments was performed in a blinded fashion. A modified Tarlov scale was employed weekly for 4 weeks [Tarlov, 1954]. Each hindlimb was rated as follows:

0 Total paraplegia of the hindlimb

1 No spontaneous movement, but responds to hindlimb pinch
2 Spontaneous movement, but unable to stand
3 Able to support weight, unable to walk on a broad, flat surface
4 Able to walk on broad, flat surface
5 Able to walk on broad, flat surface; able to support weight on a 1.8-cm-wide ledge
6 Able to walk on a 1.8 cm-wide ledge

Both the final and cumulative scores were noted, as was the ability to walk at 4 weeks. The Rivlin-Tator angleboard test was performed before the animals were sacrificed [Rivlin and Tator, 1977]. The maximum angles maintained for 5 seconds or longer in both horizontal directions were measured, then averaged, to yield a final value.

### Urodynamic Evaluation

Each of the paired bulbospongiosal muscles at the base of the urethra was punctured with platinum wire electrodes for electromyographic monitoring. These electrodes were connected to a Grass model 80 polygraph electromyograph with integrating capability.

A midline abdominal incision was made to provide access to the bladder, urethra, aorta, and femoral veins. A 24 gauge intravenous catheter was used to cannulate the aorta above the level of the iliac bifurcation. This catheter was connected using nondistensible tubing to both a Tektronix model 414 EKG/BP monitor and the Grass polygraph. The bladder was cannulated using an 18 gauge catheter, placed through an incision in the urethra below the level of the prostate gland. This catheter was connected via a Y connector to both a Harvard infusion pump and to the Grass polygraph.

A baseline measurement of heart rate and blood pressure were determined once all monitoring devices were in place. A cystometrogram was performed using a constant fill rate of 0.5 ml/second. The volume of cystometric capacity, with its corresponding intravesical pressure, was determined at the point of upward deflection of the intravesical pressure curve during the CMG. With the bladder distended at cystometric capacity, blood pressure and heart rate were again recorded. Electromyography was used throughout the investigation to monitor pelvic floor muscular activity in order to detect detrusor-external sphincter dyssynergia (DESD).

The effect of pharmacologic agents on the cardiovascular and urodynamic parameters was then undertaken. An animal was randomized to receive either terazosin (0.1 mg/kg) or diltiazem (0.5 mg/kg) intravenously via the femoral vein (9 animals in each group). In addition, an intravenous preparation of oxybutynin chloride (0.1 mg/kg) was delivered after the effects of terazosin or diltiazem had dissipated, and the rat was again exhibiting baseline blood pressure and heart rate response to bladder distention.

### Data Analysis

The paired t-test was used to compare mean blood pressure and heart rate before and during cystometrogram. ANOVA was used to compare the drugs' effect among T4, T10, and sham groups. Ordinal neurologic outcome scores were compared by the Kruskal-Wallis ANOVA followed by the Mann-Whitney U-test. All values were given as mean $\pm$ SD. A $P$ value $<0.05$ was considered significant.

**TABLE I. Animal Behavioral Data†**

| | T4 | T10 | Sham |
|---|---|---|---|
| Animal weight | 389 ± 40 | 400 ± 24 | 391 ± 35 |
| Final Tarlov score | 6* | 6* | 12 |
| Final angleboard score | 55.5 ± 6.8** | 58.3 ± 5.0** | 84.4 ± 3.0 |

†N = 18 animals in each group. Weight in grams (mean ± S.E.M.) at time of sacrifice. Tarlov score (median) prior to sacrifice (4 weeks). Angleboard score in degrees (median ± S.E.M.) prior to sacrifice (4 weeks).
*$P < 0.05$ vs. sham, Mann-Whitney U-test.
**$P < 0.05$ vs. sham, Mann-Whitney U-test.

## RESULTS

After spinal cord injury, determination of the degree of neurologic impairment was evident in a comparison of the Tarlov and Rivlin-Tator scores. The T4 animals exhibited a median Tarlov score of 6, as did the T10 animals, indicative of severe, although incomplete, spinal cord injury. A similar degree of neurologic impairment was seen in T4 and T10 animals on the inclined angleboard scores. Sham-injury rats displayed no neurologic deficiency and therefore scored a median of 12 (Table I).

Urodynamic parameters likewise reflected the degree of neurologic injury. Both T4 and T10 SCI animals demonstrated a statistically significant increase in cystometric capacity over sham controls. In addition, the maximal intravesical pressure of the T4 rats was greater than that of T10 and sham rats at cystometric capacity (Table II).

With bladder distention, the T4 animals demonstrated an elevation in mean blood pressure (MBP) from 82.9 ± 13.6 to 93.9 ± 11.3 mmHg ($P < 0.01$), while the MBP of the T10 (87.0 ± 12.3 to 87.6 ± 10.3 mm Hg, $P = 0.28$) and sham-injury animals (91.9 ± 17.9 to 92.3 ± 19 mmHg, $P = 0.30$) remained stable (Fig. 1).

With regard to heart rate (HR), the average rate of T4 animals decreased from 332.2 ± 56.5 to 311.1 ± 54.4 beats/min ($P = 0.02$) with bladder distention. The HR of T10 animals remained stable, changing from 320.0 ± 47.2 to 315.9 ± 55.3 beats/min ($P = 0.46$). The HR of sham animals also remained stable, changing from 338.6 ± 51.9 to 339.1 ± 54.1 beats/min ($P = 0.41$) with bladder distention (Fig. 2).

During cystometry, electromyography indicated a dramatic increase in pelvic floor muscular activity (DESD) during these episodes of hypertension and bradycardia in the T4-injured animals (Fig. 3A). This excessive EMG activity was also evident in the T10-level rats at the point of bladder fullness, although the level of response was more variable. Sham-injured animals failed to demonstrate these changes (Fig. 3B).

Both terazosin and diltiazem were able to abolish the increase in blood pressure and decrease in heart rate, representing autonomic dysreflexia, that occurred during bladder distention in the T4 injured animals. Blood pressure and heart rate remained stable during cystometry with the administration of terazosin and diltiazem in T10 and sham animals (Tables III and IV).

The effect of terazosin, diltiazem, and oxybutynin chloride on cystometric capacity and maximum filing pressure (the change of intravesical pressure from baseline during bladder filling) for T4, T10, and sham animals are found in Figures 4 and 5. Terazosin had no effect on cystometric capacity or maximal filling pressure

**TABLE II. Cystometric Capacity and Maximum Filling Pressure Among T4, T10, and Sham Animals†**

| | T4 | T10 | Sham |
|---|---|---|---|
| Cystometric capacity (ml) | 9.3 ± 4.3* | 6.1 ± 3.0* | 0.8 ± 0.9 |
| Maximum filling pressure (cm $H_2O$) | 39.4 ± 16.9** | 30.6 ± 8.8 | 26.7 ± 11.0 |

†N = 18 animals in each group.
*$P < 0.05$ vs. sham, ANOVA.
**$P < 0.05$ vs. sham, ANOVA.

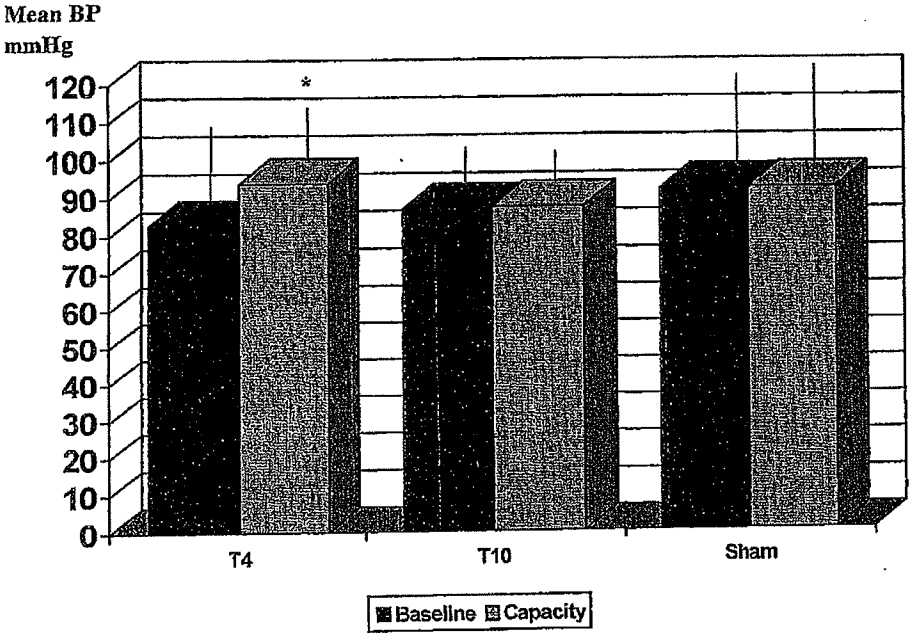


Fig. 1. Blood pressure comparison of T4, T10, and sham animals at baseline and at bladder capacity.

in T4, T10, or sham animals. Although diltiazem did not alter the maximal filling pressure in any of the three groups of animals, its administration did result in a statistical increase in cystometric capacity in T4 and T10 SCI rats but not in sham animals (Figs. 4,5).

Oxybutynin chloride demonstrated no effect on changes in blood pressure and heart rate with bladder filling in T4, T10, or sham animals (Tables III, IV). Oxybutynin chloride did affect cystometric capacity and maximal filling pressure. The T4 animals displayed an increase in cystometric capacity from 8.0 ± 4.2 to 9.0 ± 2.0 ml ($P < 0.05$), and a decrease in maximal filling pressure from 44.4 ± 20.1 to 31.3 ± 19.8 cm $H_2O$ ($P < 0.05$). The T10 cystometric capacity was not significantly altered (4.5 ± 1.7 to 5.1 ± 1.0 ml ($P = 0.44$) and maximal filling pressure remained unchanged (28 ± .7 + 5.3 to 26.7 ± 12.6 cm $H_2O$) at cystometric capacity ($P = 0.35$). In sham animals with oxybutynin administration, the bladder capacity and

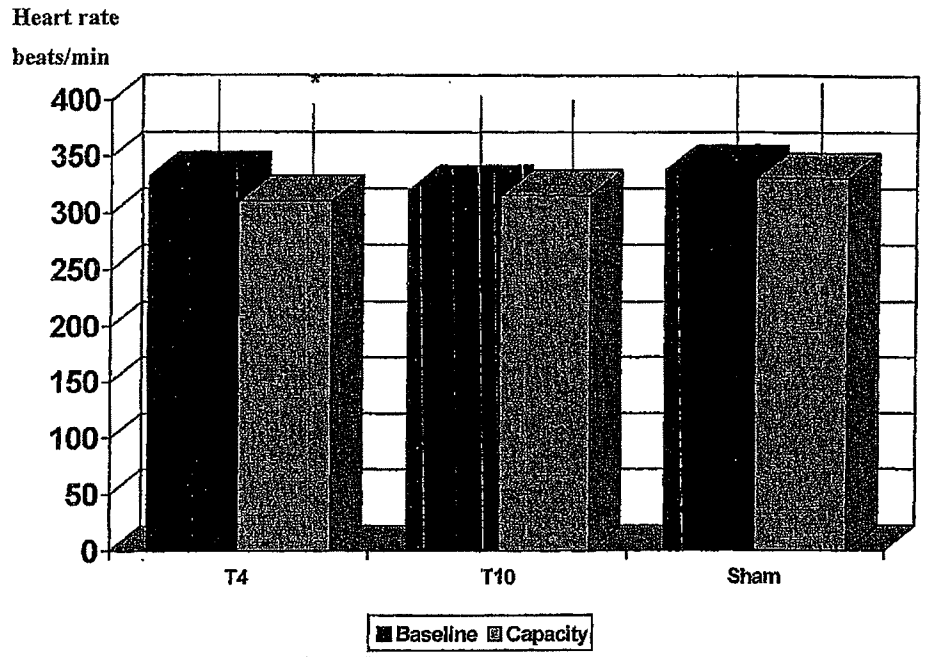


Fig. 2. Heart rate comparison of T4, T10, and sham animals at baseline and at bladder capacity.

filling pressure changed from 0.75 ± 1.1 to 1.3 ± 1.3 ml ($P < 0.05$), and 26.7 ± 9.5 to 20.1 ± 6.0 cm $H_2O$ ($P < 0.05$), respectively (Figs. 4,5).

## DISCUSSION

Autonomic dysreflexia is the development of unchecked reflex sympathetic outflow which develops in response to stimuli below the level of spinal cord injury higher than the level of T7 [Johnson et al., 1975]. Because of the dire consequences of AD, anecdotal reports of therapy effective for the control of the associated hypertension and symptoms have been published [Givre and Freed, 1989]. Ablative procedures for prevention of AD including sympathectomy, sacral neurectomy, rhizotomy, and cordectomy have been used to sever the reflex arcs of sympathetic hyperactivity, with mixed results [Trop and Bennett, 1991]. Many pharmacologic agents including hexamethonium [Kurnick, 1956], phentolamine [Sizemore and Winternitz, 1970], guanethidine [Brown et al., 1979], chlorpromazine [McGuire and Rossier, 1983], pentolinium [Trop and Bennett, 1991], diazoxide, and nitroprusside [Erickson, 1980] have been proposed, but none have become widely accepted. Treatment with phenoxybenzamine, which blocks both alpha-1 and alpha-2 adrenergic receptors, was noted to provide effective relief of symptoms of AD [McGuire et al., 1976]. This agent, however, requires multiple daily doses and has been associated with mutagenic activity in laboratory animals. Several studies reported the efficacy of

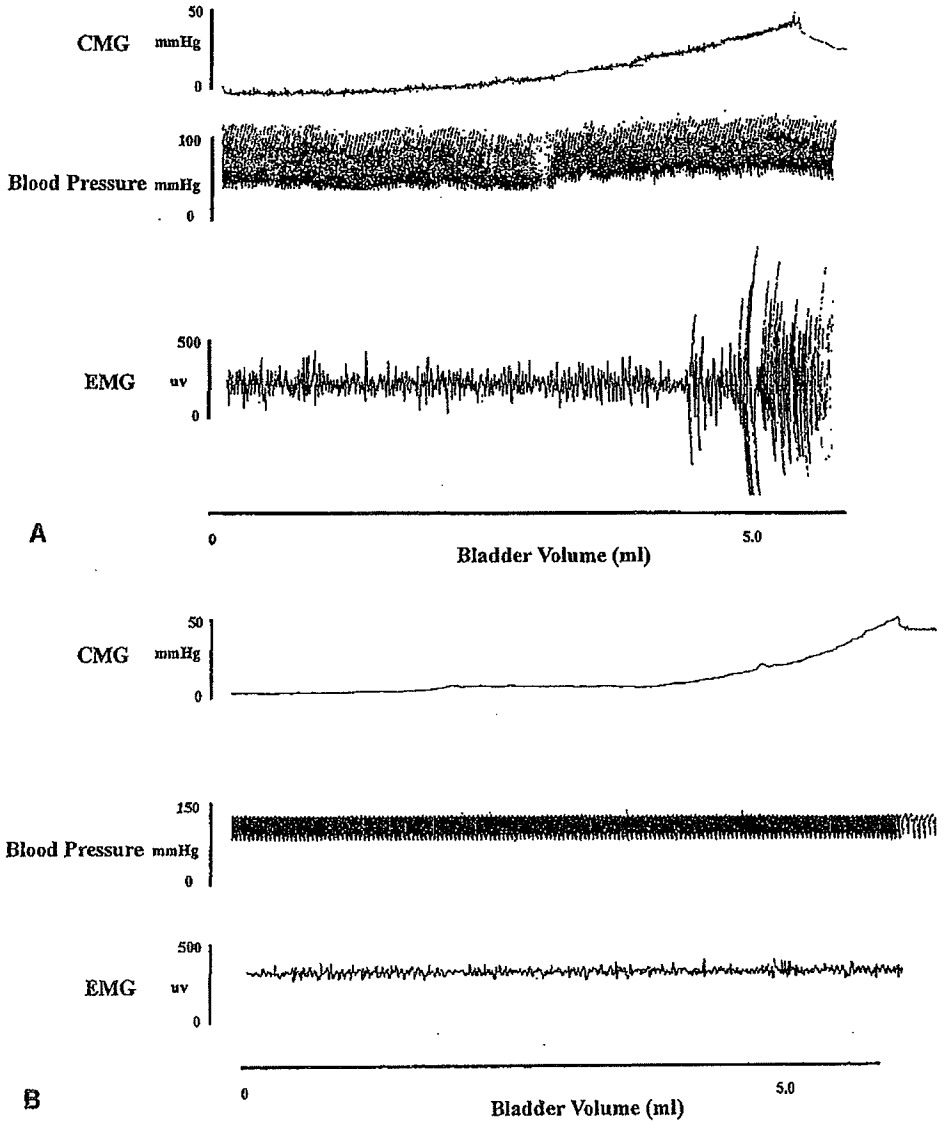


Fig. 3. Simultaneous CMG, blood pressure, and EMG tracings of (A) T4 animals demonstrating the occurrence of DESD with AD as compared to sham (B).

calcium channel blockade in the treatment of AD episodes [Lindan et al., 1985; Dykstra et al., 1987].

The development of terazosin, with its convenient once-daily dosage, has enabled more effective and better tolerated selective inhibition of alpha-1 receptors [Humphreys and Waite, 1989]. The literature also reports that diltiazem is better tolerated and may be more effective in establishing calcium channel blockade than nifedipine, especially with the formulation of slow-release preparations [Wallace et al., 1989].

**TABLE III. Effect of Pharmacologic Agents on Mean Blood Pressure Among T4, T10, and Sham Animals†**

| Mean blood pressure (mmHg) | T4 | T10 | Sham |
|---|---|---|---|
| Baseline | 82.9 ± 13.6 (n = 18) | 87.0 ± 12.3 (n = 18) | 91.9 ± 17.9 (n = 18) |
| Terazosin (0.1 mg/kg) at cystometric capacity | 84.4 ± 3.0 (n = 9) | 90.3 ± 15.0 (n = 9) | 87.5 ± 16.8 (n = 9) |
| Diltiazem (0.1 mg/kg) at cystometric capacity | 82.4 ± 13.5 (n = 9) | 86.7 ± 5.0 (n = 9) | 86.4 ± 8.3 (n = 9) |
| Oxybutynin chloride (0.1 mg/kg) at cystometric capacity | 91.5 ± 11.0* (n = 9) | 82.3 ± 10.5 (n = 9) | 88.8 ± 12.3 (n = 9) |

†No increase in mean blood pressure suggesting autonomic dysreflexia in T10 or sham animals. No statistical significant difference between baseline mean blood pressure at cystometric capacity after administration of terazosin and diltiazem.
*Oxybutynin chloride did not blunt blood pressure elevation at cystometric capacity vs. baseline ($P < 0.05$).

**TABLE IV. Effect of Pharmacologic Agents on Heart Rate Among T4, T10, and Sham Animals†**

| Heart rate (beats/min) | T4 | T10 | Sham |
|---|---|---|---|
| Baseline | 333.2 ± 56.5 (n = 18) | 320.0 ± 47.2 (n = 18) | 338.6 ± 51.9 (n = 18) |
| Terazosin (0.1 mg/kg) at cystometric capacity | 344.0 ± 23.0 (n = 9) | 340.3 ± 15.0 (n = 9) | 355.5 ± 26.8 (n = 9) |
| Diltiazem (0.1 mg/kg) at cystometric capacity | 319.5 ± 28.5 (n = 9) | 320.5 ± 35.0 (n = 9) | 320.0 ± 66.8 (n = 9) |
| Oxybutynin chloride (0.1 mg/kg) at cystometric capacity | 294.0 ± 33.0* (n = 9) | 315.8 ± 25.4 (n = 9) | 325.5 ± 35.5 (n = 9) |

†No decrease in heart rate suggesting autonomic dysreflexia in T10 or sham animals. No statistical significant difference between baseline heart rate at cystometric capacity after administration of terazosin and diltiazem.
*Oxybutynin chloride did not blunt heart rate depression at cystometric capacity vs. baseline ($P < 0.05$).

The rat model of spinal cord injury (SCI) effectively demonstrated impaired somatomotor and autonomic nervous system functions resulting from SCI. Altered Tarlov and Rivlin-Tator angleboard scores quantified the degree of impaired somatomotor function. Animals that had received either a T4 or T10 SCI demonstrated not only a significantly elevated cystometric capacity, but also an elevated intravesical pressure at cystometric capacity.

The rats which underwent sham injury displayed no altered hemodynamic parameters during cystometrographic evaluations. Despite a documented spinal cord injury, T10 level rats also maintained stable blood pressure and heart rate during bladder filling. T4 level injured rats, however, further demonstrated altered physiology of the autonomic nervous system. Those animals manifested statistically significant elevations in mean systemic blood pressure in response to the stimulus of bladder distention accompanied with decrease in heart rate. These simultaneous changes of the two hemodynamic parameters parallel the development of hypertension and reflex bradycardia noted in those human SCI patients with autonomic dys-

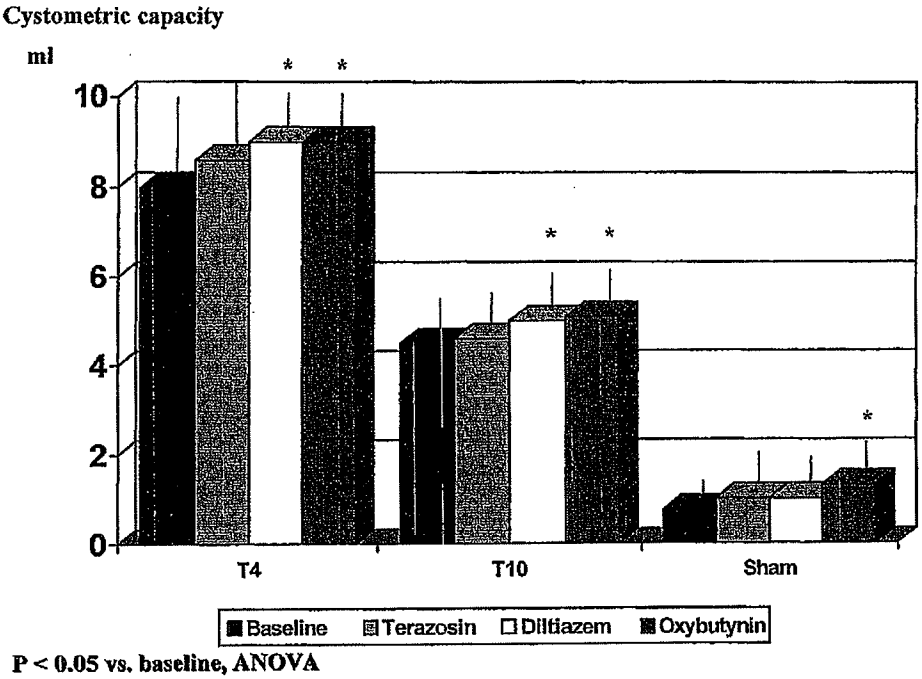


Fig. 4. Cystometric capacity (ml) of T4, T10, and sham rats at baseline vs. capacity after terazosin, diltiazem, and oxybutynin chloride administration.

reflexia. Thus, the rat model of blunt SCI adequately replicates AD development as seen in human subjects.

Previous investigation has documented the development of autonomic dysreflexia in transected SCI animals subjected to increased intravesical pressures while conscious [Osborn et al., 1990]. Our experiments have demonstrated a similar response despite pentobarbital anesthesia and an incomplete SCI.

The use of terazosin provided effective therapy, abolishing the AD response. The use of diltiazem likewise prevented the development of AD parameters. The administration of alpha-1 blockade and calcium channel blockade exhibited no effect in those animals with a lower level SCI or sham injury. The use of these medications in patients with high SCI would be appropriate therapy as prophylaxis against, as well as treatment for, the development of AD and its sequelae. Further clinical research in the use of these two agents should establish their use in those patients predisposed to the development of autonomic dysreflexia.

During the course of the investigation, it became evident that excessive pelvic floor muscular activity occurred with the AD response (Fig. 1). We feel that this represents the development of dyssynergy between activity of the external urinary sphincter and the detrusor. Such detrusor-sphincter dyssynergia is widely recognized in human subjects with SCI (Kaplan et al., 1991). Interestingly, our investigation indicated that DESD was present in all of the high-level SCI animals, but its occurrence in the lower-level animals was more variable. We postulate that, in those subject to AD, the development of AD frequently accompanies the development of

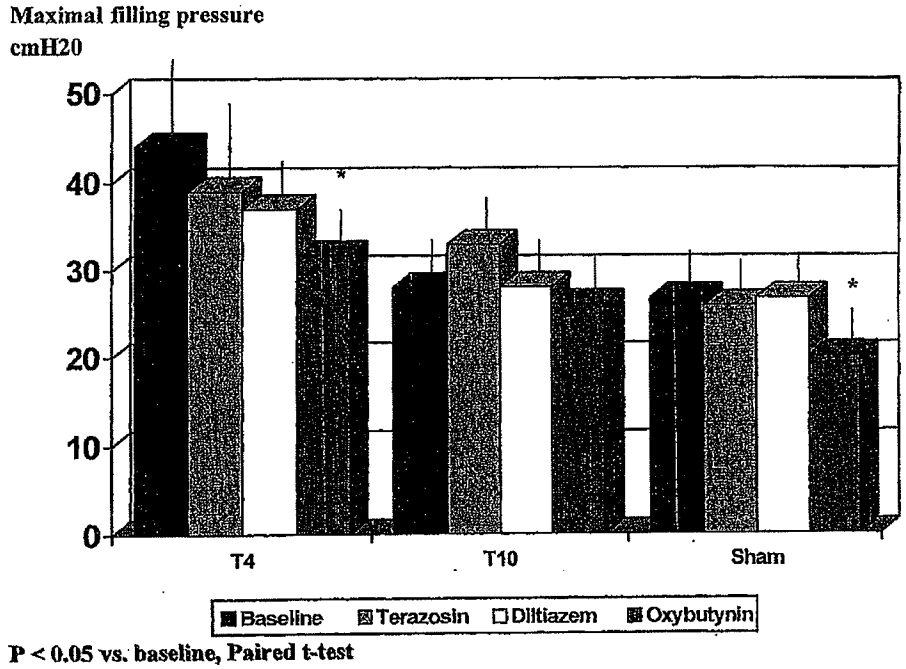


Fig. 5. Maximum filling pressure (cm $H_2O$) of T4, T10, and sham rats at baseline vs. that after terazosin, diltiazem, and oxybutynin chloride administration.

DESD. Alternatively, DESD may occur even though an animal is not subject to the AD response. The administration of the anticholinergic agent oxybutinin demonstrated the ability to increase the cystometric capacity and decrease the maximal intravesical pressure at capacity in not only the sham-injury animals, but also T4 and T10 SCI rats. Oxybutynin alone did not blunt autonomic dysreflexia.

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